REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application is respectfully requested.

Applicants note with appreciation the courtesies extended to applicant and applicant's representatives during a teleconference interview held on July 16, 2002. During the interview, applicant's position that weight should be given to the recitation of "mucoadhesive" in the preamble was discussed. The fact that Constancis fails to disclose mucoadhesive polymers as claims was also discussed. Applicant's proposed adding new claims in Jepson format, as are presented herein. No agreement was reached, however.

Claims 30, 50, 72, 74, 75, 82, 96 and 99 have been rejected under 35 U.S.C. § 112, second paragraph, for purportedly being indefinite. This rejection is respectfully traversed.

It is respectfully submitted that these claims would be sufficiently clear to a person skilled in the art reading the claims in light of the specification. Applicants' specification clearly defines the term "derivative," as used in the claims. "Derivatives" as used in the claims is defined in the paragraph bridging pages 4-5 of the specification. The claim encompasses "derivatives [of the thiolated polymer] obtained by auto-cross-linking, introduction of functional groups, attachment of complexing agents (such as, e.g., EDTA), coupling of enzyme inhibitors, etc., in particular in case of polymers comprising negatively charged groups, e.g. COO^- groups." It allegedly is not clear which "functional groups" are included in the definition. Specific examples of functional groups are given in the specification, *e.g.*, at page 10. Here, carboxyl groups and amino groups are defined as

"functional groups." With respect to "derivatives" as used in claim 96, one skilled in the art would recognize that any known cysteine derivative, e.g., homocystein, N-acetylcysteine, cysteinemethylester, could be used in the instant invention. As described in the specification, the important chemical property of the cysteine and cysteine derivative for purposes of the invention is the compound has a functional amino group and is a thiol-containing compound. This would be clear to a person skilled in the art at the very least based on the description at page 9, last paragraph - page 10, second paragraph.

Since the claims when read in light of the specification would be sufficiently clear to a person skilled in the art, withdrawal of the rejection is respectfully requested and believed to be in order.

In view of the above, withdrawal of the rejection of record is respectfully requested and believed to be in order.

Claims 1 and 28-32 have been rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by Constancis et al (U.S. Patent No. 5,496,872). This rejection is respectfully traversed.

The Federal Circuit has previously held that prior art is anticipatory only if every element of the claimed invention is disclosed in a single item of prior art in the form literally defined in the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986), *cert denied*, 480 US 947 (1987). This standard is clearly not met in the instant application.

By contrast with the polymers of Constancis, the claimed invention is directed to a "mucoadhesive polymer comprising not more than 10 different monomers and at least one

non-terminal thiol group." The polymers of Constancis will not be "mucoadhesive" as recited in applicants' claims. Instead, the polymers of Constancis are "bioadhesive," and are "glues." *See, e.g.*, col. 5, lns. 3-5. The "bioadhesives" and "mucoadhesives" are two distinct classes of compounds. The compounds used by Constancis may be used *in vitro* or *in vivo* for binding biological tissues to each other or for binding a biological tissue and, e.g., an implanted biomaterial. *See, e.g.*, col. 5, lns. 47-49. The mucoadhesive polymers are intended to bind to the mucus gel layer and not to a tissue.

The term "mucoadhesive" in the preamble must be considered in evaluating the claims. Limitations in the preamble are considered where such limitations are necessary to give meaning to the claim and properly define the invention. *Perkin Elmer Corporation v. Computervision Corporation*, 221 USPQ 669, 675 (Fed. Cir. 1984). Moreover, if the specification makes clear that the inventors were working on a particular problem, the claims will be read in light of the specification and will include the preamble to give "life and meaning " to the claims. *See, Corning Glass Works v. Sumitomo Electric USA, Inc.*, 9 USPQ2d 1962 (CAFC 1989)

Mucoadhesive polymers have particular properties, which differ from those of bioadhesives. Mucus is a loosened, extremely wide meshed network which is characteristic for the mucus layers. Unlike for bioadhesives, a tight binding of a polymer molecule to the (tissue) surface adjacent to the mucus is neither necessary nor desired for a mucoadhesive polymer. A covalent binding of the mucoadhesive polymer directly to the tissue surface could have extremely negative effects. Mucoadhesive polymers thus should specifically bind to the mucus layer above the tissue in these areas. With a mucus turnover of about 6-

8 hours, adverse effects obtained by binding are prevented by covalently linking the mucoadhesive polymers to the mucus rather than the tissue itself. *See, e.g.*, page 2, first paragraph.

The instant invention relates to mucoadhesive polymers having improved properties. The improved mucoadhesive polymers "enable a targeted introduction of active substance in mucus layers, wherein a stable presence at the target site shall be enabled." By this invention, an effective and efficient active substance delivery system is proved "by which an improved and thus also extended adhesion of drug on the mucosae can be attained." Page 2, ¶2, of the application.

The term "mucoadhesive" is recognized in the art. It is a term of art that is used to describe a particular class of polymers. U.S. Patent No. 5,047,244, for example, defines "mucoadhesive"as being "a material that adheres to a mucosal tissue surface in-vivo and/or in-vitro. Such adhesion will adherently localize the dosage form onto the mucus membrane and requires the application of a force of at least about 50 dynes/cm^2 to separate the mucoadhesive material from the mucus membrane." Col.3, lns. 20-27. *See,* Bernkop-Schnurch, Declaration, ¶7. The term "mucoadhesive," as used in the instant application, is a polymer that adheres to the mucus layer covering a mucosal tissue surface in-vivo and/or in-vitro. Such adhesion has to be higher than at least 83 μJ for the total work of adhesion (TWA) described for tensile studies with dry compacts, according to Bernkop-Schnürch et al. *Pharm. Res.* 16, 1999, 876-881. *See*, Bernkop-Schnurch, Declaration, ¶8.

Mucoadhesive polymers are recognized in the art as including polyacrylates, (e.g., carbomer, polycarophil, carbopol, etc.), cellulose derivatives (e.g., sodium

carboxymethylcellulose, hydroxypropylcellulose, etc.), hyaluronic acid, alginate, pectin and chitosan. *See, e.g.,* Bernkop-Schnürch, A. (2002). *Mucoadhesive Polymers In: Polymeric Biomaterials* 2nd edition (Ed. Severian Dumitriu) Marcel Dekker, New York.

Hagerstrom H, Edsman K. "Interpretation of mucoadhesive properties of polymer gel preparations using a tensile strength method." *J Pharm Pharmacol* 2001 Dec; 53(12):1589-99

Eouani C, Piccerelle P, Prinderre P, Bourret E, Joachim J. "In-vitro comparative study of buccal mucoadhesive performance of different polymeric films." *Eur J Pharm Biopharm* 2001 Jul; 52(1):45-55;

Singla AK, Chawla M, Singh A. "Potential applications of carbomer in oral mucoadhesive controlled drug delivery system: a review." *Drug Dev Ind Pharm* 2000 Sep; 26(9):913-24;

Kerec M, Bogataj M, Mugerle B, Gasperlin M, Mrhar A. "Mucoadhesion on pig vesical mucosa: influence of polycarbophil/calcium interactions." *Int J Pharm* 2002 Jul 8; 241(1):135-43;

Solomonidou D, Cremer K, Krumme M, Kreuter J. "Effect of carbomer concentration and degree of neutralization on the mucoadhesive properties of polymer films." *J Biomater Sci Polym Ed* 2001;12(11):1191-205;

Adriaens E, Remon JP, Ludwig A. "Evaluation of a mucoadhesive tablet for ocular use." Ceulemans J, Vermeire A, *J Control Release* 2001 Dec 13; 77(3):333-44;

Bernkop-Schnurch A, Gilge B., "Anionic mucoadhesive polymers as auxiliary agents for the peroral administration of (poly)peptide drugs: influence of the gastric juice." *Drug Dev Ind Pharm.* 2000 Feb; 26(2):107-13.

Constancis does not disclose or suggest such "mucoadhesive" polymers, as instantly claimed. Constancis instead relates to "biocompatible and biodegradable surgical adhesives based on non-toxic products." Col. 1, lns. 39-42. More specifically, Constancis discloses biological "glues or gluing material." Col. 5, lns. 24-25. "It is obvious that nobody would use a surgical adhesive to try to connect one mucus gel layer with another, or to try to connect a mucus gel layer with a tissue." *See,* Bernkop-Schnurch, Declaration, ¶10.

Thus, the bioadhesives of Constancis are not "mucoadhesives." Bernkop-Schnurch Declaration, ¶10. This would be apparent to a person skilled in the art. For example, Constancis' bioadhesives would not adhere to the mucosa with the same strength as a mucoadhesive polymer, for example, as taught by the '244 Patent. This is because they do not fulfill the minimal criteria to be mucoadhesive. For instance, in the teaching book *Drug Delivery Systems* (Ellis Horwood, New York), G. Hunt, P. Kearney and I. Kellaway defined criteria for polymers to be mucoadhesive in the chapter "Mucoadhesive polymers in drug delivery systems" as follows:

- Strong H-bonding groups (-OH, -COOH)
- Strong anionic charges
- Sufficient flexibility to penetrate the mucus network
- Surface tension characteristics suitable for wetting mucus/mucosal tissue surfaces

- High molecular weight

In contrast to the mucoadhesive polymers as instantly claimed, not even a single point out of these five is fulfilled by the monomers/polymers described by Constancis. *See,* Bernkop-Schnurch, Declaration, ¶11.

The instant invention relates to the surprising discovery that by introducing at least one non-terminal thiol group into a mucoadhesive polymer having not more than 10 different monomers, the mucoadhesive properties of the polymer are greatly improved. This discovery was unexpected. Dr. Bernkop-Schnurch discovered that the mucoadhesive polymers having the non-terminal thiol group could form reversible, covalent bonds with the cysteine-rich subdomains of the mucus glycoproteins (*see,* Figure 1 of the application). These bonds allow for a stable localization of the polymers on the mucus layer of certain mucosal membranes. *See also,* page 3 of the application. *See also,* Bernkop-Schnurch, Declaration, ¶12.

As stated by Dr. Bernkop-Schnurch, unexpectedly, the mucoadhesive polymers of the invention have significantly improved binding capacity to intestinal mucosa. *See,* Bernkop-Schnurch, Declaration, ¶13. As stated *supra*, the most frequently used mucoadhesive polymers are polymers such as mentioned in claim 3 of the instant application, *e.g.,* polyacrylates (Carbomer, Polycarbophil, Carbopol, *etc.*), cellulose derivatives (sodium carboxymethylcellulose, hydroxypropylcellulose, *etc.*), hyaluronic acid, alginate, pectin and chitosan.

The improved properties of the claimed mucoadhesive polymers can be seen by comparing the total work of adhesion of mucoadhesive polymers modified in accordance

with the invention with that for unmodified polymers. This can be done by reference to the following table:

Polymer	Total work of adhesion in μJ; means ± SD (n= 3-8)	Reference
polycarbophil		A. Bernkop-Schnürch, V. Schwarz, S. Steininger, Polymers with thiol groups: a new generation of mucoadhesive polymers? Pharm. Res. 16 (1999) 876-881.
thiolated polycarbophil	280 ±68	
sodium carboxymethyl cellulose	108 ±17	A. Bernkop-Schnürch, S. Steininger, Synthesis and characterisation of mucoadhesive thiolated polymers, Int. J. Pharm. 194 (2000) 239-247.
thiolated sodium carboxymethyl cellulose	157 ±6	
chitosan HCl	23 ±10	C.E. Kast, A. Bernkop-Schnürch, Thiolated polymers: development and in vitro evaluation of chitosan-thioglycolic acid conjugates, Biomaterials 22 (2001) 2345-2352.
thiolated chitosan	234 ±0	
sodium alginate	26 ±1	A. Bernkop-Schnürch, C.E. Kast, M.F. Richter, Improvement in the mucoadhesive properties of alginate by the covalent attachment of cysteine, J. Control. Release 71 (2001) 277-285.
thiolated sodium alginate	102 ±36	

As confirmed by Dr. Bernkop-Schnurch, this strong improvement in the mucoadhesive properties was unexpected. *See,* Bernkop-Schnurch, Declaration, ¶15. It is based on thiol/disulfide exchange reactions between the polymer and the mucus layer. Prior to the instant invention, there was nothing reported in the literature about thiolated mucoadhesive polymers. This can be seen based upon the reviewer's report of the first publication submitted about thiolated mucoadhesive polymers. In the top-journal for this research field (*Pharmaceutical Research*) it is written about a "brilliant idea." Nor is anything reported about this mechanism by Constancis et al.

As shown in the above table, the TWA values for the claimed thiolated polymers are increased 50% to over 100% by introducing the non-terminal thiol group. As stated in Dr. Bernkop-Schnurch's Declaration, this strong improvement in the mucoadhesive properties was unexpected. *See also,* Bernkop-Schnurch, Declaration, ¶15.

New claims 100-108 further distinguish over Constancis. Claim 100 relates to the claimed polymers, however, the claim is written in Jepson format. Using this format, "indicates intent to use the preamble to define the claimed invention." *Catalina Marketing International v. Coolsavings.com*, 62 USPQ2d 1781, 1785 (Fed. Cir. 2002), *citing Rowe v. Dror,* 42 USPQ2d 1550 (Fed. Cir. 1997) and *Epcon Gas Sys., Inc. V. Bauer Compressors, Inc.,* 61 USPQ2d 1470, 1475 (Fed. Cir. 2002). "[W]hen the claim drafter chooses to use *both* the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." *Catalina Marketing,* 62 USPQ2d at 1785, *quoting Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995). Thus, these

new claims in particular evidence that patentable weight should be given to the recitation of "mucoadhesive" in the preamble of the claim.

In failing to describe mucoadhesive polymers having non-terminal thiol groups, Constancis fails to describe or render obvious applicants' claimed invention. Withdrawal of the rejection under §102(b) is thus respectfully requested and believed to be in order.

Claims 1 and 28-99 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Bernkop-Schnurch et al (*Intl. J. Pharm. 157*:17-25 (1997) and *Intl. J. Pharm. 146*:247-254 (1997)) in view of Constancis et al (U.S. Patent No. 5,646,239). This rejection is respectfully traversed.

As noted by the Examiner, Bernkop-Schnurch discloses mucoadhesive polymers, however, the reference fails to disclose polymers having thiol groups as in the instant invention. Constancis is cited for its teaching of modification of biomaterials with thiolated compounds. However, as noted above, Constancis fails to disclose or even suggest modification of mucoadhesive polymers. There is no suggestion in Constancis to modify a mucoadhesive polymer to contain at least one non-terminal thiol group. Constancis instead discloses bioadhesive substances having polysulfide crosslinking moieties.

Since Constancis is unrelated to mucoadhesive substances, first there would be no motivation for the combination proposed in the Official Action. One skilled in the art would not be motivated to change the polymers of Bernkop-Schnurch and add thiol groups based on the disclosure of Constancis. The principle of binding of bioadhesives is based, according to Constancis, on a diffusion process of the monomers/oligomers into the tissue followed by a stabilizing polymerization process via oxidation of the thiol groups. This is

similar to the principle used in other "super glues," such as glues based on cyanoacrylates which diffuse into surfaces and subsequently polymerize. The goal for bioadhesion is to achieve a very tight and strong connection of the bioadhesive with a given cell or tissue surface or to achieve a strong connection between cell or tissue surfaces. The "goal" for the compounds of Constancis is thus to adhere directly to the tissue.

By contrast, "mucoadhesion," as in Bernkop-Schnurch and the instant invention, is based on a different scientific concept. Mucus is a loosened, extremely wide meshed network which is characteristic for the mucus layers. A tight binding of a polymer molecule to the (tissue) surface adjacent to the mucus is, therefore, neither necessary nor desired for a mucoadhesive polymer. A covalent binding of the mucoadhesive polymer directly to the tissue surface could have extremely negative effects. For example, a covalent binding of a perorally administered drug to the epithelial cells of the gastrointestinal tract would lead to an obstruction of bowels. Mucoadhesive polymers thus should specifically bind to the mucus layer above the tissue in these areas. With a mucus turnover of about 6-8 hours, the above-described effect (e.g., obstruction of bowels) is prevented by covalently linking the mucoadhesive polymers to the mucus rather than the tissue itself. Please note Figure 1 from Muller and Hildebrand, "Pharmazeutische Technologie: Moderne Arznelformen," Wissenschaftilche Veriagagesellschaft mbH Stuttgart (1997), Stuttgart, Germany, p. 280, which illustrates the adhesion of a mucoadhesive polymer to the mucus gel layer.

The compounds used by Constancis may be used *in vitro* or *in vivo* for binding biological tissues to each other or for binding a biological tissue and, e.g., an implanted

biomaterial. The mucoadhesive polymers are intended to bind to the mucus gel layer and not to a tissue. This object of the bioadhesives as in Constancis is thus completely different from the object of mucoadhesive polymers, as described for applicants invention in the instant specification. *See, e.g.*, page 2, first paragraph. Thus, there would have been no motivation for one skilled in the art to combine the cited art of Bernkop-Schnurch and Constancis as proposed in the Official Action.

As recognized by the Federal Circuit, there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself. *In re Oetiker*, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992). In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the examiner to provide a reason *why* one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Nesbit*, 25 USPQ2d 1817, 1819 (BPAI 1992). As stated above, in the present case, no such motivation exists.

The binding of the mucoadhesive polymers as claimed is based on a completely different and novel mechanism for mucoadhesion. Applicants' invention is based on the observation that the mucus consists of mucus glycoproteins, which are connected with each other via numerous disulfide bonds. By the addition of a thiolated mucoadhesive polymer, new disulfide bonds are formed via thiol/disulfide exchange reactions between the polymer and the mucus glycoproteins. This mechanism is illustrated in the enclosed Figure 2. This mechanism has previously never been proposed or reported in the field of mucoadhesive

polymers. As noted by the Examiner, Bernkop-Schnurch do not disclose or suggest thiol-group containing polymers. As Constancis is unrelated to mucoadhesive polymers, this mechanism also is not disclosed or suggested in this reference.

Prior to the instant invention, the formation of secondary bond formation was regarded as the principle source of mucoadhesion. *See, e.g.*, Hunt et al, "Mucoadhesive Polymers in Drug Delivery Systems," in Drug Delivery Systems, Ellis Horwood, New York). That carboxyl groups in their non-ionized form are capable of strong hydrogen bond formation was regarded as a substantial reason for the mucoadhesive properties of such substances. *See,* Hunt, p. 186, third paragraph, which states:

> In accordance with the theory that secondary bond formation is the principal source of mucoadhesion, those polymers with carboxyl groups present are all, without exception, mucoadhesive. The carboxyl group in its unionized form is capable of strong H-bond formation, and in its ionized form also able to interact electrostatically. However, the functional groups on the polymer backbone should not be in such close proximity that they interfere with each other (e.g. by intramolecular H-bonding). As the carboxyl concentration along a polymer chain decreases, for example, in moving from sodium alginate to Karya gum to gelatin, the mucoadhesive strength also decreases.

With respect to mucoadhesion, it is further stated that the direct interaction with the tissue or membrane surface is, in contrast with bioadhesion, not of relevance for mucoadhesion. *See, e.g.,* Hunt, p. 184, second paragraph, last sentence.

It should further be noted that ***none*** of the mucoadhesive polymers known in the art prior to the instant invention, as evidenced by Hunt, Table 1 and Figure 1, contained any thiol groups. This evidences that the role of thiol groups in the process of mucoadhesion was neither known nor proposed prior to applicants' invention. Even in mucoadhesive polymers based on proteins, no free thiol groups are present (such polymers would also

have more than 10 different monomers). *See, e.g.*, Hunt, page 190, wherein the amino acid composition of gelatine is listed and cysteine residues are not even listed under amino acids with "low abundance." Moreover, as stated *supra*, the incorporation of thiol groups into mucoadhesive polymers was deemed a "brilliant idea." *See, Pharmaceutical Research* and Bernkop-Schnurch Declaration, ¶15.

Figure 1 of Hunt makes clear that the compounds regarded as the most potent mucoadhesive polymers in the prior art did not contain any thiol groups, much less "at least one non-terminal thiol group" as instantly claimed. It was thus surprising to applicants that by providing non-terminal thiol groups in such mucoadhesive polymers, the mucoadhesive properties of such polymers could be enormously improved. Indeed, the thiolated mucoadhesive polymers of the instant invention have mucoadhesion properties that are significantly superior to the best mucoadhesive polymers known in the art.

Therefore, even if Constancis taught polymers having non-terminal thiol groups, there would have been no motivation for one skilled in the art to incorporate thiol groups into mucoadhesive polymers to achieve the instant invention.

Moreover, even if the cited art were combined, unexpected results are achieved by the instant invention. As shown in the Bernkop-Schnurch Declaration, unexpected results are achieved by incorporating non-terminal thiol groups into a mucoadhesive polymer. *See, e.g.*, Bernkop-Schnurch Declaration, ¶¶13-15. That the TWA could increase 50 to over 100% by adding the non-terminal thiol groups would not have been expected.

In view of the above, withdrawal of the rejection of record under §103(a) is thus respectfully requested and believed to be in order.

Further and favorable action in the form of a Notice of Allowance is respectfully requested. Such action is believed to be in order.

In the event that there are any questions relating to this amendment or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (508) 339-3684 so that prosecution may be expedited.

Respectfully submitted,

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